INDENE DERIVATIVES AND PROCESS FOR THE PREPARATION THEREOF

FIELD OF THE INVENTION

The present invention relates to a novel indene derivative, which is useful as a modulator of a peroxisome proliferator activated receptor (PPAR), a process for the preparation thereof and a pharmaceutical composition containing same as an active ingredient.

BACKGROUND OF THE INVENTION

Peroxisome proliferator activated receptors (PPARs) are members of the nuclear hormone receptor superfamily and function as transcription factors regulating gene expression in a form of heterodimers with retinoid X receptors (RXRs). The PPARs are divided into three subtypes, "PPARα ", "PPARγ " and "PPARδ ", and are generally involved in maintaining energy homeostasis in vertebrates through the control of fat and glucose metabolisms.

Accordingly, many attempts have been made to develop PPARα and PPARγ full agonists which are useful for the treatment and prevention of disorders modulated by PPARs, e.g., metabolic syndromes such as diabetes, obesity, arteriosclerosis, hyperlipidemia, hyperinsulinism and hypertension; inflammatory diseases such as osteoporosis, liver cirrhosis and asthma; and cancer.

For example, it has been reported that thiazolidine-2,4-dione (TZD) and non-TZD-based full agonists on PPARγ exhibit excellent blood glucose level-lowering effect in non-insulin dependent diabetes mellitus (NIDDM) mammal models (*J. Med. Chem.*, **1999**, 42, 3785.; *Bioorg. Med. Chem. Lett.*, **2000**, 2453.; *Chem. Pharm. Bull.*, **2002**, 50, 1349.; *Bio. Med. Chem. Lett.*, **2002**, 77.; *J. Med. Chem.*, **2003**, 46, 3581.).

However, such a PPARγ full agonist is also known to cause adverse side effects including weight gain due to facilitation of fat cell differentiation, cardiac hypertrophy, edema and liver damage.

Therefore, there exists a need to develop selective PPAR modulators (SPPARMs) which are capable of selectively controlling activities of the PPARs without causing side effects (*Molecular Cell*, **2001**, 8, 737; *Molecular Endocrinology*, **2003**, 17, 662; *Molecular Endocrinology*, **2002**, 16, 2628).

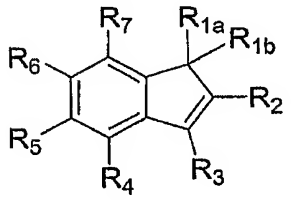
SUMMARY OF THE INVENTION

Accordingly, it is a primary object of the present invention to provide a novel compound, which is capable of selectively modulating the activities of peroxisome proliferator activated receptors (PPARs), causing no adverse side effects.

It is another object of the present invention to provide a process for the preparation of said compound.

It is a further object of the present invention to provide a pharmaceutical composition containing said compound as an active ingredient.

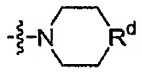
In accordance with one aspect of the present invention, there is provided a novel indene derivative of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein,

R_{1a} is OH or H;

R_{1b} is C_{1-6} alkyl, C_{3-6} cycloalkyl, benzyl or phenyl, the phenyl being optionally substituted with one or more substituents selected from the group consisting of halogen, CN, NH_2, NO_2 and OR^a, when R_{1a} is OH; when R_{1a} is H, R_{1b} is OR^a, NR^bR^c, $NHCOR^a$ or  ;

R_2 is CN, CO_2R^a or $CONR^eR^f$;

R_3 is phenyl optionally substituted with one or more substituents selected from the group consisting of halogen, CN, NH_2, NO_2, OR^a and C_{1-6} alkyl; and

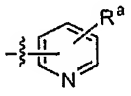
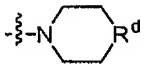
R^4, R^5, R^6 and R^7 are each independently H, $O(CH_2)_mR^g$ or CH_2R^h;

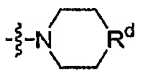
in which

R^a is H, C_{1-6} alkyl or C_{3-6} cycloalkyl, the C_{1-6} alkyl and C_{3-6} cycloalkyl being optionally substituted with one or more halogens;

R^b, R^c, R^e and R^f are each independently H, C_{1-6} alkyl, C_{3-6} cycloalkyl or benzyl;

R^d is O, S or NR^a;

R^g is H,  ,  or phenyl, the phenyl being optionally substituted with one or more substituents selected from the group consisting of halogen, CN, NH_2 and NO_2;

R_h is  ; and

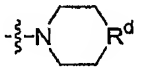
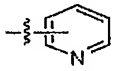
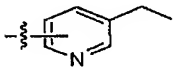
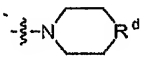
m is an integer in the range of 1 to 3.

DETAILED DESCRIPTION OF THE INVENTION

The indene derivatives of the present invention may include optical isomers of the compound of formula (I).

Also, the pharmaceutically acceptable salt of the inventive indene

derivative is a non-toxic addition salt generated from an inorganic acid such as hydrochloric acid, an organic acid such as trifluoroacetic acid, citric acid, lactic acid, maleic acid and fumaric acid, an inorganic base such as an alkali or alkaline earth metal (e.g., sodium, potassium, magnesium and calcium) hydroxides, bicarbonates and carbonates, or an organic base such as amines.

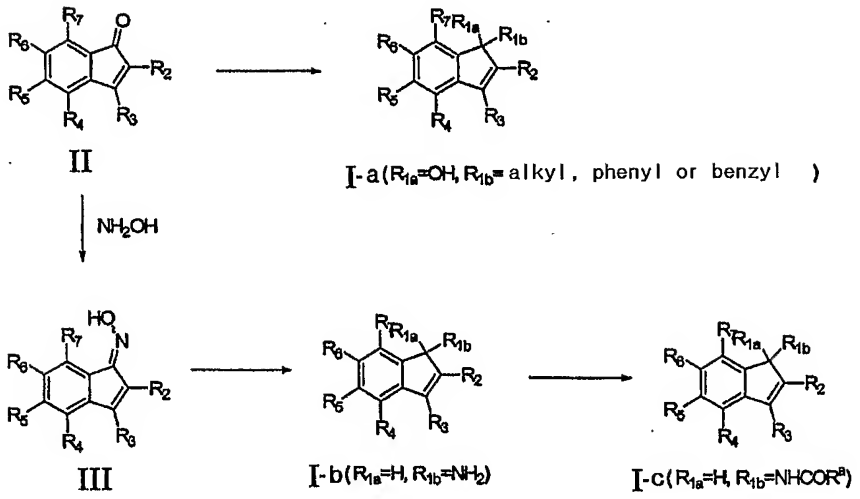
Among the compounds of formula (I) of the present invention, preferred are those wherein R_{1b} is C_{1-6} alkyl, C_{3-6} cycloalkyl, benzyl or phenyl, the phenyl being optionally substituted with one or more methoxy groups, when R_{1a} is OH; when R_{1a} is H, R_{1b} is OR^a, NR^bR^c, $NHCOR^a$ or  ; R_3 is phenyl being optionally substituted with one or more halogens or C_{1-4} alkyls; and R_4 and R_7 is H, in which R^a is H or C_{1-6} alkyl; R^d is O or S; R^g is H, phenyl,  ,  or  .

More preferred are those wherein R_3 is phenyl; R_5 is H; and R_6 is $O(CH_2)_mR^g$ or CH_2R^h.

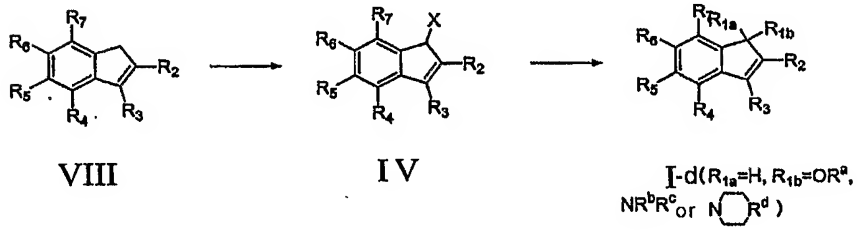
The present invention also provides processes for preparing indene derivatives of formula (I).

The inventive compound of formula (I) may be prepared, for example, as shown in Reaction Schemes 1 or 2 as described below:

Reaction Scheme 1



Reaction Scheme 2



wherein, R_{1a}, R_{1b}, R_2, R_3, R_4, R_5, R_6 and R_7 have the same meanings as defined in formula (I), and X is halogen.

In Reaction Scheme 1, the compound of formula (I-a), i.e., a compound formula (I) wherein R_{1a} is OH and R_{1b} is alkyl, phenyl or benzyl, may be prepared by reacting the compound of formula (II) with RMgX or RLi (R=alkyl or aryl, and X=halogen), preferably with a Grignard reagent (RMgX) in a solvent.

The solvent that can be used in this reaction is tetrahydrofuran (THF) or diethyl ether, and the reaction may be carried out at a temperature in the range of 0℃ to room temperature for 1 hour or less.

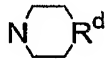
Further, in Reaction Scheme 1, the compound of formula (I-b), i.e., a

compound formula (I) wherein R_{1a} is H and R_{1b} is NH_2, may be prepared by (1a) reacting the compound of formula (II) with hydroxyl amine to obtain the corresponding compound of formula (III), and (1b) reacting the compound of formula (III) with hydrogen in the presence of catalyst, e.g., Pt/C, Pd or Raney nickel.

Reaction (1a) may be conducted in a solvent, e.g., methanol or ethanol at a temperature in the range of room temperature to the boiling point of the solvent until the compound of formula (II) is entirely consumed. In reaction (1b), hydrogen may be provided using a balloon and the reaction may be carried out using a solvent, e.g., methanol or ethanol at a temperature in the range of 10 to 30℃ for 1 to 24 hours.

Also, as shown in Reaction Scheme 1, the compound of formula (I-c), i.e., a compound formula (I) wherein R_{1a} is H and R_{1b} is $NHCOR^a$, may be prepared by reacting the compound of formula (I-b) with acetyl chloride or anhydrous acetic acid in a solvent in the presence of a base.

The solvent that can be used in the reaction is dichloromethane, chloroform or dichloroethane, and the base may be triethylamine, pyridine or diisopropylethylamine, and the reaction may be carried out at a temperature in the range of 0 to 40°C for 1 min to 12 hours.

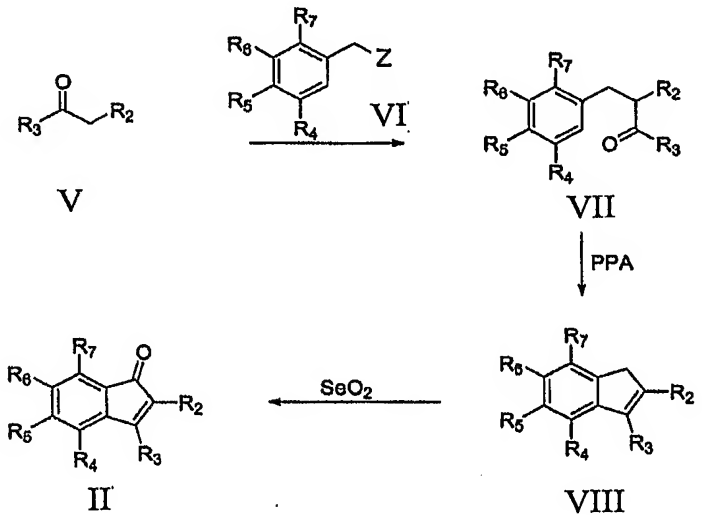
In Reaction Scheme 2, the compound of formula (I-d), i.e., a compound formula (I) wherein R_{1a} is H and R_{1b} is OR^a, NR^bR^c or  , may be prepared by (2a) halogenating the compound of formula (VIII) using a radical halogenating agent, e.g., N-bromosuccinimide (NBS) or N-chlorosuccinimide (NCS), in the presence of a radical initiator such as azobisisobutyronitrile (AIBN) to obtain the compound of formula (IV), and (2b) reacting the compound of formula (IV) with an appropriate amine or alcohol in the presence of an inorganic compound, e.g., $AgNO_3$ or silver(I) triflate.

Reaction (2a) may be conducted in a solvent, e.g., dichloromethane,

chloroform or dichloroethane at a temperature in the range of room temperature to the boiling point of the solvent for 1 to 24 hours, and reaction (2b) may be conducted in a solvent, e.g., tetrahydrofuran, methanol or ethanol at a temperature in the range of 10 to 70℃ for 1 to 24 hours.

The compounds of formula (II) and (VIII) used as starting materials in preparing the compounds of formula (I-a), (I-b), (I-c) and (I-d) may be prepared by the method described in *Tetrahedron*, **1995**, 51, 12179; *J. Org. Chem.*, **1993**, 58, 4579; *J. Chem. Soc., Perkin Trans I.*, **1992**, 2985; *Synthesis,* **1991,** 115&176; *J. Med. Chem.*, **1988,** 31, 1316&1754, as shown in Reaction Schemes 3 to 6.

Reaction Scheme 3



wherein, R_2, R_3, R_4, R_5, R_6 and R_7 have the same meanings as defined in formula (I), and Z is halogen or a leaving group such as OMs

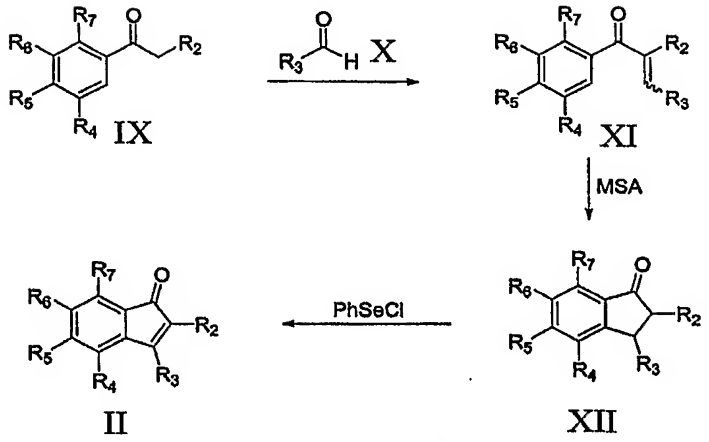
In Reaction Scheme 3, the compound of formula (II) may be prepared by (3a) reacting the compound of formula (V) with the compound of (VI) in the presence of a base to obtain the corresponding compound of formula (VII), (3b) cyclizing the compound of formula (VII) to form a cyclic compound of formula

(VIII), and (3c) oxidizing the compound of formula (VIII).

The solvent which can be used in reaction (3a) includes a polar solvent such as DMF, and the base may be an inorganic base such as K_2CO_3, and reaction (3a) may be carried out at 20 to 50℃ for 3 to 15 hours, using the inorganic base in an amount ranging from 2 to 10 equivalents and can be facilitated by the addition of sodium iodide in an amount ranging from 1 to 3 equivalents based on the amount of the compound of formula (V). In reaction (3b), the cyclization of the compound of formula (VII) may be conducted in a solvent, e.g., polyphosphoric acid (PPA), polyphosphoric acid/xylene, methane sulfonic acid (MSA) or pyridinium toluene sulfonate (PPTS) in an amount ranging from 5 to 10 equivalents based on the amount of the compound of formula (VII), at a temperature in the range of 30 to 50℃ for 3 to 12 hours. Further, in reaction (3c), the oxidization of the compound of formula (VIII) may be carried out in a solvent, e.g., 1,4-dioxane or THF, at a temperature in the range of 50 to 120℃ for 7 to 15 hours, using a conventional oxidizing agent, preferably, selenium dioxide in an amount ranging from 5 to 15 equivalents based on the amount of the compound of formula (VIII).

Also, the compounds of formula (V) and (VI) used as starting materials in Reaction Scheme 3 are commercially available or they may be easily prepared in accordance with the conventional procedures disclosed in *Indian J. Chem. Sect. B*, **1983**, *22*, 830.

Reaction Scheme 4



wherein, R_2, R_3, R_4, R_5, R_6 and R_7 have the same meanings as defined in formula (I).

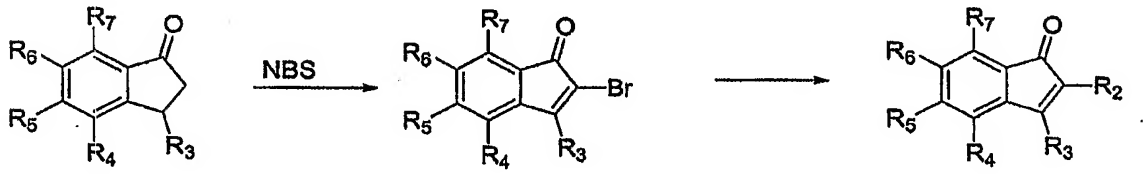
In Reaction Scheme 4, the compound of formula (II) may be prepared by (4a) reacting the compound of formula (IX) with the compound of formula (X) in the presence of a base to obtain the corresponding compound of formula (XI), (4b) cyclizing the compound of formula (XI) to form a cyclic compound of formula (XII), and (4c) oxidizing the compound of formula (XII).

The solvent which can be used in reaction (4a) includes a polar solvent such as DMF, ethanol and nitroethane, and the base may be an inorganic base such as sodium hydroxide, or an organic base such as piperidine, and this condensation reaction (4a) may be carried out at 20 to 80℃ for 3 to 15 hours, using the base in an amount ranging from 2 to 5 equivalents based on the amount of the compound of formula (IX). In reaction (4b), the cyclization of the compound of formula (VII) may be conducted in a solvent, e.g., dichloromethane, chloroform, carbon tetrachloride or xylene, at 20 to 50℃ for about 3 to 12 hours in the presence of methane sulfonic acid (MSA), pyridinium toluene sulfonate (PPTS) or polyphosphoric acid (PPA). In reaction (4a), if the compound of formula (IX) is reacted with the compound of formula (X) in anhydrous nitroethane in the

presence of ammonium chloride under a nitrogen gas atmosphere, the above condensation and cyclization reactions (4a) and (4b) may be conducted in one pot to obtain the compound of formula (XII). Further, in reaction (4c), the compound of formula (XII) is oxidized using phenyl selenium chloride and hydrogen peroxide in the presence of an amine such as pyridine, to obtain the compound of formula (II). Phenyl selenium chloride and the amine base may be used in amounts ranging from 1 to 3 equivalents and 1 to 5 equivalents, respectively, based on the amount of the compound of formula (XII), and an excess amount of 30%-hydrogen peroxide may be used in this reaction, which may be carried out in a solvent, e.g., dichloromethane, chloroform, 1,4-dioxane or carbon tetrachloride, at 20 to 70℃ for 3 to 15 hours.

Further, the compounds of formula (IX) and (X) used as starting materials in Reaction Scheme 4 are commercially available.

Reaction Scheme 5



XIII XIV II

wherein, R_2, R_3, R_4, R_5, R_6 and R_7 have the same meanings as defined in formula (I).

In Reaction Scheme 5, the compound of formula (II) may be prepared by (5a) bromination of the compound of formula (XIII) to obtain the compound of formula (XIV) and (5b) introducing R_2 to the compound of formula (XIV).

In reaction (5a), the compound of formula (XIII) is brominated in carbon tetrachloride using NBS in an amount of 1 to 3 equivalents based on the compound of formula (XIII), to obtain the compound of formula (XIV), and the

reaction may be conducted at 50 to 100℃ for about 0.5 to 3 hours, while irradiating infrared ray with a lamp or using a radical initiator such as AIBN. Further, in reaction (5b), the compound of formula (II) may be prepared by conducting the conventional palladium-catalyzed C-C coupling reaction, e.g., Suzuki reaction or Heck reaction as described in *Tetrahedron Lett.* **2003**, *44*, 7095 and *Org. Lett.* **2004**, *6*, 1577, or by reacting the compound of formula (XIV) with an appropriate R_2-containing nucleophile at 70 to 150℃ for 3 to 15 hours in the presence of copper(I) cyanide or sodium methane sulfonate in an amount of 1 to 5 equivalents based on the amount of the compound of formula (XIV) using a polar solvent such as nitroethane and DMF.

Suitable processes for preparing the compound of formula (II) as shown in Reaction Scheme 6 are as follows.

Reaction Scheme 6

XV II

wherein, R_2, R_3, R_4, R_5, R_6 and R_7 have the same meanings as defined in formula (I); Y is OH, SH, NH_2, C_{1-6} alkyl or halogen; and n is an integer in the range of 0 to 5.

Method 1): Useful processes when Y is OH, SH or NH_2

The compound of formula (II) may be prepared by conducting conventional acylation or alkylation reactions as described in *J. Org. Chem.* **1988**, *53*, 3321 and *Tetrahedron Lett.* **2003**, *44*, 4199.

Specifically, the compound of formula (XV) may be reacted with an appropriate carboxylic acid or an acyl chloride under conventional reaction conditions, using a condensation agent such as dicyclohexyl carbodiimide (DCC)

in an amount of about 1 equivalent based on the amount of the compound of formula (XV), to give the compound of formula (II).

The acylation reaction may be conducted in a solvent, e.g., dichloromethane, at room temperature for 1 to 12 hours, when a carboxylic acid is used; and when an acyl chloride is used, the reaction may be conducted at 0 to 30℃ for 1 to 5 hours in the presence of an amine base such as triethylamine.

Alternatively, the compound of formula (II) may be prepared by conducting conventional alkylation reactions, e.g., Mitsunobu reaction as described in *Eur. J. Med. Chem. Chim. Ther.* **2000**, *35*, 53. Specifically, the compound of formula (XV), an alcohol, triphenyl phosphine and diethyl azodicarboxylate (DEAD) may be dissolved in a solvent, e.g. THF, and stirred at 0 to 30℃ for 3 to 12 hours, to give the compound of formula (II).

In addition, the compound of formula (II) may be prepared by reacting the compound of formula (XV) with an alkyl halide in a solvent, e.g., acetone or N,N-dimethyl formamide at 20 to 100℃ for 3 to 12 hours in the presence of a base such as NaH, K_2CO_3 and NaOH.

Method 2): Useful processes when Y is C_{1-6} alkyl

The compound of formula (II) may be prepared by conducting a conventional halogenation reaction comprising , e.g., the steps of (6a) reacting the compound of formula (XV) with a radical halogenating agent such as N-bromosuccinimide (NBS) and N-chlorosuccinimide (NCS) in the presence of a radical initiator such as AIBN, to obtain a halogenated intermediate, and (6b) reacting the resulting intermediate with a suitable alkyl, aryl or heterocyclic compound having a substituent selected from the group consisting of OH, NH_2, SH and CO_2H.

Reaction (6a) may be conducted in a solvent, e.g., carbon tetrachloride, at 50 to 100℃ for 0.5 to 3 hours, and reaction (6b) may be conducted in a solvent, e.g., dichloromethane, THF or DMF, at 0 to 70℃ for 1 to 7 hours, using an

inorganic base such as K_2CO_3 or an organic base such as triethylamine in an amount ranging from 1 to 3 equivalents based on the amount of the halogenated intermediate obtained in step (6a). Reaction (6b) can be facilitated by the addition of sodium iodide in an amount ranging from 1 to 3 equivalents based on the amount of the halogenated intermediate.

Method 3): Useful processes when Y is halogen

The compound of formula (II) may be prepared by conducting conventional palladium-catalyzed C-C coupling reactions, e.g., Suzuki reaction, Heck reaction or Stille reaction as described in Reaction Scheme 5, using the compound of formula (XV) as a starting material.

Exemplary compounds of formula (I) of the present invention which can be prepared in accordance with the methods described above are listed in Table 1:

Table 1

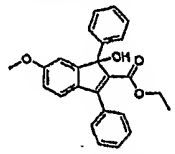
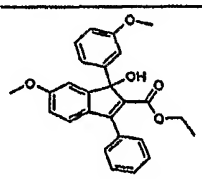
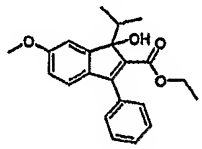
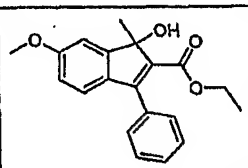
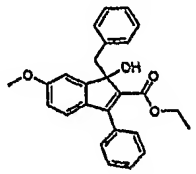
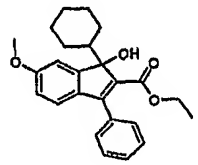
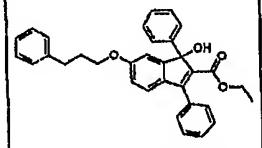
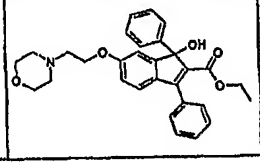
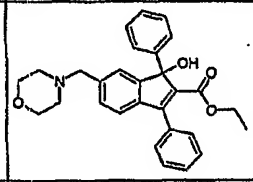
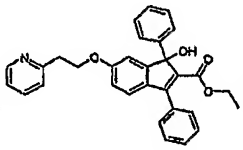
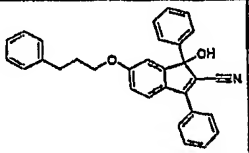
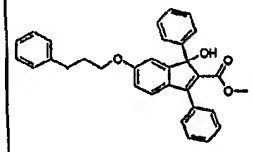
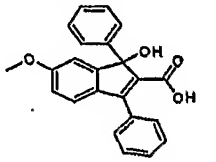
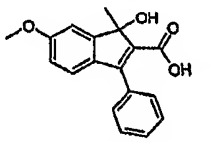
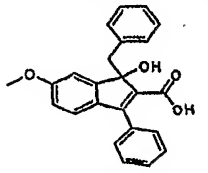
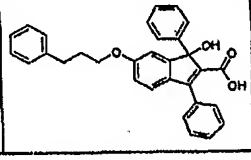
Ex-No.	Structure	^{1}H-NMR ($CDCl_3$, 200 MHz) δ
1		7.53-7.46 (m, 5H) 7.31-7.24 (m, 5H) 7.11 (d, *J* = 8.4 Hz, 1H) 6.85-6.79 (m, 2H) 4.45 (s, 1H) 4.09-3.91 (m, 2H) 3.76 (s, 3H) 0.92 (t, *J* = 7.2 Hz, 3H)
2		7.51-7.46 (m, 5H) 7.26-7.07 (m, 4H) 6.86 (d, *J* = 2.4 Hz, 1H) 6.78-6.75 (m, 2H) 4.45 (s, 1H) 4.09-3.91 (m, 2H) 3.81 (s, 3H) 3.76 (s, 3H) 1.00 (t, *J* = 7.2 Hz, 3H)
3		7.43-7.34 (m, 5H) 7.26 (s, 1H) 7.02 (d, *J* = 8.4 Hz, 1H) 6.79 (dd, *J* = 2.3 Hz, *J* = 8.4 Hz, 1H) 4.10-4.06 (m, 2H) 3.86 (s, 3H) 2.57 (sept, *J* = 6.8 Hz, 1H) 1.22 (d, *J* = 6.8 Hz, 3H) 1.00 (t, *J* = 7.2 Hz, 3H) 0.69 (t, *J* = 6.8 Hz, 3H)
4		7.44~6.79(m, 8H), 4.10(q, *J*=7.2 Hz, 2H), 3.88(s, 3H), 1.78(s, 3H), 1.06(t, *J*=7.2 Hz, 3H)
5		7.35~6.77(m, 13H), 4.13(q, *J*=7.2 Hz, 2H), 4.05(s, 1H), 3.85(s, 3H), 3.48(s, 2H), 1.05(t, *J*=7.2 Hz, 3H)
6		7.51~6.75(m, 8H), 4.12~4.02(m, 2H), 3.94(s, 1H), 3.86(s, 3H), 2.17~1.08(m, 10H), 1.00(t, *J*=7.2 Hz, 3H)
7		7.63~6.73(m, 18H), 4.47(s, 1H), 4.11(q, *J*=7.2 Hz, 2H), 4.07~3.88(m, 2H), 2.75(t, *J*=7.6 Hz, 2H), 2.07~2.00(m, 2H), 0.93(t, *J*=7.2 Hz, 3H)
8		7.68~6.75(m, 13H), 4.43(s, 1H), 4.04~4.00(q, *J*=7.2 Hz, 2H), 4.01~3.93(m, 2H), 3.69(t, *J*=4.9 Hz, 4H), 2.73(t, *J*=5.1 Hz, 2H), 2.51(t, *J*=4.9 Hz, 4H), 0.92(t, *J*=7.2 Hz, 3H); mp 121-123℃

Table 1 (Continued)

Ex-No.	Structure	^{1}H-NMR ($CDCl_3$, 200 MHz) δ
9		7.60-7.06 (m, 13H) 3.95-4.05 (m, 2H) 3.60-3.80 (m, 4H) 3.45 (s, 2H) 2.30-2.43 (m, 4H) 0.92 (t, *J* = 7.3 Hz, 3H)
10		8.53-8.49 (m, 1H) 7.59-7.51 (m, 6H) 7.48-7.06 (m, 8H) 6.85-6.74 (m, 2H) 4.35-4.27 (m, 2H) 4.00-3.92 (m, 2H) 3.19 (t, *J* = 6.5 Hz, 2H) 0.92 (t, *J* = 7.3 Hz, 3H)
11		7.70-6.90 (m, 18H) 3.95 (t, *J* = 6.2 Hz, 2H) 2.77 (t, *J* = 7.4 Hz, 2H) 2.10-2.04 (m, 2H)
12		7.50~6.72(m, 18H), 4.01(t, *J*=6.0 Hz, 2H), 3.52(s, 3H), 2.75(t, *J*=7.2 Hz, 2H), 2.10-2.04(m, 2H)
13		7.46~6.73(m, 13H), 3.75(s, 3H)
14		7.45~6.80(m, 8H), 3.88(s, 3H), 1.78(s, 3H)
15		7.39~6.78(m, 13H), 3.87(s, 3H), 3.50(s, 2H)
16		7.45~6.77(m, 18H), 4.05~3.87(m, 2H), 2.76(t, *J*=7.4 Hz, 2H), 2.06~2.01(m, 2H)

5

Table 1 (Continued)

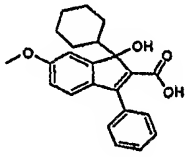
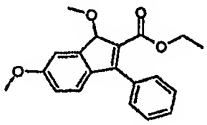
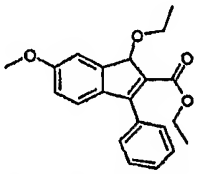
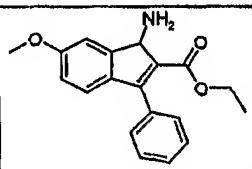
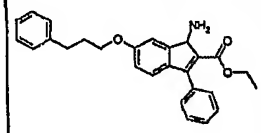
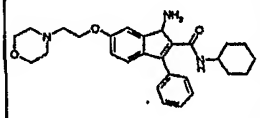
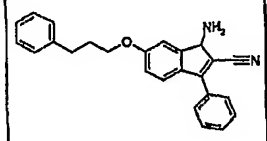
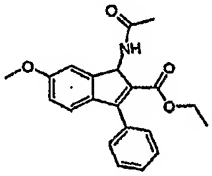
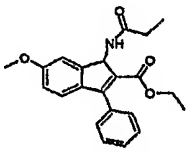
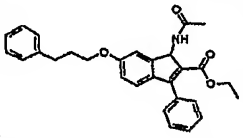
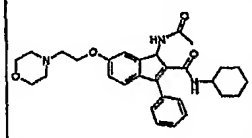
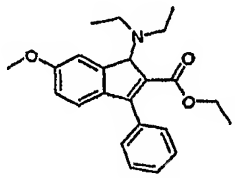
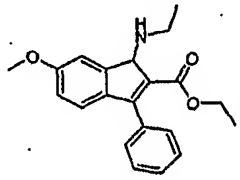
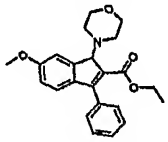
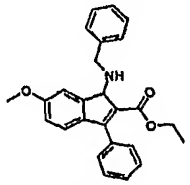
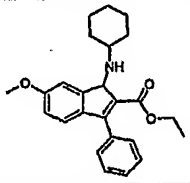
Ex-No.	Structure	^{1}H-NMR ($CDCl_3$, 200 MHz) δ
17		7.53~6.77(m, 8H), 3.86(s, 1H), 2.23~0.88(m, 11H)
18		7.51-7.41 (m, 5H) 7.17 (d, *J* = 2.4 Hz, 1H) 7.10 (d, *J* = 8.4 Hz, 1H) 6.83 (dd, *J* = 8.4, 2.4 Hz, 1H) 5.48 (s, 1H) 4.22-4.09 (m, 2H) 3.87 (s, 3H) 3.30 (s, 3H) 1.12 (t, *J* = 7.2 Hz, 3H)
19		7.51-7.42 (m, 5H) 7.16 (s, 1H) 7.08 (d, *J* = 8.3 Hz, 1H) 7.82 (dd, *J* = 8.3, 2.3 Hz, 1H) 5.49 (s, 1H) 4.24-4.07 (m, 2H) 3.86 (s, 3H) 3.64-3.49 (m, 2H) 1.22 (t, *J* = 7.0 Hz, 3H) 1.13 (t, *J* = 7.1 Hz, 3H)
20		7.22-7.06 (m, 6H) 6.92-6.86 (m, 2H) 6.04 (brs, NH_2) 4.72 (s, 1H) 4.11-4.03 (m, 2H) 3.84 (s, 3H) 1.05 (t, *J* = 7.2 Hz, 3H)
21		7.29-7.04 (m, 11H) 7.04-6.85 (m, 2H) 6.01 (brs, 2H) 4.71 (s, 1H) 4.12-3.95 (m, 4H) 2.81 (t, *J* = 7.2 Hz, 2H) 2.11 (qujnt, *J* = 7.2 Hz, 2H) 1.05 (t, *J* = 7.2 Hz, 3H)
22		7.32-7.16 (m, 5H) 7.01 (d, *J* = 8.3 Hz, 1H) 6.92 (d, *J* = 2.2 Hz, 1H) 6.82 (dd, *J* = 2.2 8.3 Hz, 1H) 6.25 (brs, 2H) 4.54 (s, 1H) 4.10-4.20 (m, 3H) 3.74 (t, *J* = 4.6 Hz, 4H) 2.81 (t, *J* = 5.7 Hz, 3H) 2.54 (t, *J* = 4.6 Hz, 4H) 0.70-1.46 (m, 10H)
23		7.34-7.09 (m, 11H) 6.93-6.83 (m, 2H) 4.89 (s, 2H) 3.99 (t, *J* = 6.5 Hz, 2H) 2.82 (t, *J* = 6.5 Hz, H) 2.10 (qujnt, *J* = 6.5 Hz, 2H)
24		10.47 (brs, 1H) 7.86 (d, J = 2.4 Hz, 1H) 7.24-7.17 (m, 3H) 7.04-7.01 (m, 3H) 6.89 (dd, *J* = 8.4, 2.4 Hz, 1H) 4.72 (s, 1H) 4.13-4.01 (m, 2H) 3.85 (s, 3H) 2.32 (s, 3H) 1.04 (t, *J* = 7.2 Hz, 3H)

Table 1 (Continued)

Ex-No.	Structure	^{1}H-NMR ($CDCl_3$, 200 MHz) δ
25		10.52 (brs, 1H) 7.92 (d, J = 2.2 Hz, 1H) 7.21-7.16 (m, 3H) 7.04-7.00 (m, 3H) 6.88 (dd, *J* = 8.1, 2.4 Hz, 1H) 4.71 (s, 1H) 4.11-4.02 (m, 2H) 3.85 (s, 3H) 2.58 (q, *J* = 15.1, 7.5 Hz, 2H) 1.34 (t, *J* = 7.4 Hz, 3H) 1.04 (t, *J* = 7.1 Hz, 3H)
26		10.45 (brs, 1H) 7.85 (d, *J* = 2.4 Hz, 1H) 7.31-7.17 (m, 10H) 7.02 (d, *J* = 8.4 Hz, 1H) 6.89 (dd, *J* = 2.4, 8.4 Hz, 1H) 4.71 (s, 1H) 4.12-3.99 (m, 4H) 2.82 (t, *J* = 7.2 Hz, 2H) 2.33 (s, 3H) 2.11 (qujnt, *J* = 7.2 Hz, 2H) 1.04 (t, *J* = 7.2 Hz, 3H)
27		11.62 (s, 1H) 7.88 (d, *J* = 2.4 Hz, 1H) 7.33-7.26 (m, 5H) 7.15 (d, *J* = 7.4 Hz, 1H) 6.97-6.83 (m, 1H) 5.29 (d, 6.82 *J* = 6.0 Hz, 1H) 4.10-4.20 (m, 3H) 3.68-3.65 (m, 4H) 2.81 (t, *J* = 5.7 Hz, 2H) 2.54-2.59 (m, 4H) 2.31 (s, 3H) 0.70-1.46 (m, 10H)
28		7.45-7.00 (m, 7H) 6.80 (dd, *J* = 8.4, 2.4 Hz, 1H) 4.77 (s, 1H) 4.02-3.92 (m, 2H) 3.83 (s, 3H) 3.60 (q, *J* = 14.4, 7.2 Hz, 4H) 1.20 (t, *J* = 6.9 Hz, 6H) 0.98 (t, *J* = 7.2 Hz, 3H)
29		7.35 (d, *J* = 2.1 Hz, 1H) 7.21-7.06 (m, 6H) 6.86 (dd, *J* = 8.4, 2.4 Hz, 1H) 4.68 (s, 1H) 4.07-3.94 (m, 4H) 3.83 (s, 3H) 1.42 (t, *J* = 7.2 Hz, 3H) 1.00 (t, *J* = 7.2 Hz, 3H)
30		7.21-7.02 (m, 7H) 6.82 (dd, *J* = 8.4, 2.4 Hz, 1H) 4.77 (s, 1H) 4.00-3.90 (m, 6H) 3.82 (s, 3H) 3.73-3.65 (m, 2H) 3.57-3.52 (m, 2H) 0.97 (t, *J* = 7.2 Hz, 3H)
31		8.37 (brs, 1H) 7.44-7.14 (m, 12H) 7.05 (d, *J* = 8.7 Hz, 1H) 5.00 (d, *J* = 6.3 Hz, 2H) 4.70 (s, 1H) 4.04-3.98 (m, 2H) 3.64 (s, 3H) 1.00 (t, *J* = 7.2 Hz, 3H)
32		7.21-7.05 (m, 7H) 7.86 (dd, *J* = 8.4, 2.1 Hz, 1H) 4.66 (s, 1H) 4.07-3.96 (m, 3H) 3.83 (s, 3H) 2.21-2.13 (m, 2H) 1.88-1.83 (m, 2H) 1.69-1.26 (m, 6H) 1.00 (t, *J* = 7.2 Hz, 3H)

The above compounds of the present invention are as follows:

1) 1-hydroxy-6-methoxy-1,3-diphenyl-1H-indene-2-carboxylic acid ethyl ester

2) 1-hydroxy-6-methoxy-1-(3-methoxy-phenyl)-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

3) 1-hydroxy-1-isopropyl-6-methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

4) 1-hydroxy-6-methoxy-1-methyl-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

5) 1-benzyl-1-hydroxy-6-methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

6) 1-cyclohexyl-1-hydroxy-6-methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

7) 1-hydroxy-1,3-diphenyl-6-(3-phenyl-propoxy)-1H-indene-2-carboxylic acid ethyl ester

8) 1-hydroxy-6-(2-morpholine-4-yl-ethoxy)-1,3-diphenyl-1H-indene-2-carboxylic acid ethyl ester

9) 1-hydroxy-6-morpholine-4-yl-methyl-1,3-diphenyl-1H-indene-2-carboxylic acid ethyl ester

10) 1-hydroxy-1,3-diphenyl-6-(2-pyridine-2-yl-ethoxy)-1H-indene-2-carboxylic acid ethyl ester

11) 1-hydroxy-1,3-diphenyl-6-(3-phenyl-propoxy)-1H-indene-2-carbonitrile

12) 1-hydroxy-1,3-diphenyl-6-(3-phenyl-propoxy)-1H-indene-2-carboxylic acid methyl ester

13) 1-hydroxy-6-methoxy-1,3-diphenyl-1H-indene-2-carboxylic acid

14) 1-hydroxy-6-methoxy-1-methyl-3-phenyl-1H-indene-2-carboxylic acid

15) 1-benzyl-1-hydroxy-6-methoxy-3-phenyl-1H-indene-2-carboxylic acid

16) 1-hydroxy-1,3-diphenyl-6-(3-phenyl-propoxy)-1H-indene-carboxylic

acid

17) 1-cyclohexyl-1-hydroxy-6-methoxy-3-phenyl-1H-indene-2-carboxylic acid

18) 1,6-dimethoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

19) 1-ethoxy-6-methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

20) 1-amino-6-methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

21) 1-amino-3-phenyl-6-(3-phenyl-propoxy)-1H-indene-2-carboxylic acid ethyl ester

22) 1-amino-6-(2-morpholin-4-yl-ethoxy)-3-phenyl-1H-indene-2-carboxylic acid cyclohexyl amide

23) 1-amino-3-phenyl-6-(3-phenyl-propoxy)-1H-indene-2-carbonitrile

24) 1-acetylamino-6-methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

25) 6-methoxy-3-phenyl-1-propionylamino-1H-indene-2-carboxylic acid ethyl ester

26) 1-acetylamino-3-phenyl-6-(3-phenyl-propoxy)-1H-indene-2-carboxylic acid ethyl ester

27) 1-acetylamino-6-(2-morpholin-4-yl-ethoxy)-3-phenyl-1H-indene-2-carboxylic acid cyclohexyl amide

28) 1-diethylamino-6-methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

29) 1-ethylamino-6-methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

30) 6-methoxy-1-morpholin-4-yl-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

31) 1-benzyl amino-6-methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

32) 1-cyclohexyl amino-6-methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

The inventive indene derivative of formula (I) and a pharmaceutically

acceptable salt thereof is capable of selectively modulating activities of PPARs, and thus it causes no adverse side effects such as weight gain, cardiac hypertrophy, edema and liver damage.

The present invention also includes within its scope a pharmaceutical composition comprising a therapeutically effective amount of the novel compounds of formula (I), as defined above, or a pharmaceutically acceptable salt thereof as an active ingredient together with a pharmaceutically acceptable carrier.

The inventive pharmaceutical composition is useful for the treatment and prevention of disorders modulated by PPARs, i.e., metabolic syndromes such as diabetes, obesity, arteriosclerosis, hyperlipidemia, hyperinsulinism and hypertension; inflammatory deseases such as osteoporosis, liver cirrhosis and asthma; and cancer.

The pharmaceutical compositions of the invention may be formulated for administration orally or parenterally, including intravenous, intraperitoneal, subcutaneous, rectal and topical routes of administration. The composition for oral administration may take various forms such as tablets, soft and hard gelatin capsules, aqueous solutions, suspensions, emulsions, syrups, granules and elixirs, which may contain conventional additives such as a diluent (e.g., lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and glycine), a lubricant (e.g., silica, talc, stearic acid or its magnesium and calcium salts and polyethylene glycol). In the case of the tablet form, the composition may further comprise a binder (e.g., magnesium aluminum silicate, starch paste, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose and polyvinyl pyrrolidone) and optionally a disintegrant (e.g., starch, agar and alginic acid or its sodium salt), absorbent, colorant, flavor, sweetener and the like.

The composition may be sterilized and/or contain an adjuvant such as a preservative, stabilizer, wetting agent, emulsifier, a salt for controlling an osmotic pressure and/or a buffer solution, and other pharmaceutically effective materials.

The inventive compounds may be administered as an active ingredient in an effective amount ranging from about 0.1 to 500 mg/kg, preferably from about 0.5 to 100 mg/kg per day in a single dose or in divided doses.

The following Preparations and Examples are given for the purpose of illustration only and are not intended to limit the scope of the invention.

Preparation Example 1: Preparation of 6-methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

Step 1) Preparation of 2-(3-methoxy-benzyl)-3-oxo-3-phenyl-propionic acid ethyl ester

Ethylbenzoyl acetate (7g, 36.42mmol), potassium carbonate (15.1g, 109.26 mmol) and sodium iodide (6.55g, 43.70mmol) were dissolved in N,N-dimethyl formamide and the mixture was stirred at room temperature. 3-Methoxybenzyl chloride (6.274g, 40.06mmol) was added thereto followed by stirring for 1hr at room temperature. The resulting mixture was washed with saturated ammonium chloride and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 10.69g of the titled compound.

^{1}H-NMR (200MHz, $CDCl_3$) δ 7.96(dd, J=6.8Hz, J=7.2Hz, 2H), 7.56(m, 1H) 7.24(d,J=10.6Hz, 1H), 6.84～6.69(m, 3H), 4.63(t, J=7.3Hz, 1H), 4.16～4.06(m, 2H), 3.76(s, 3H), 3.31(d, J=6.8Hz, 2H), 1.13(t, J=7.1Hz, 3H)

Step 2) Preparation of 6-methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

The compound (10.69g, 34.26mmol) obtained in Step 1 was mixed with 100g of poly phosphoric acid, and stirred for 1hr at 30~45°C. The resulting dark

mud-color solution was washed with water and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 4.064g of the titled compound (yield: 40%) as a white solid.

^{1}H-NMR (200MHz, $CDCl_3$) δ 7.46~7.40(m, 5H), 7.20(q, J=10.8Hz, 2H), 6.87(dd, 8.6Hz, J=2.3Hz, 1H), 4.13(q, J=7.2Hz, 2H), 3.86 (s, 3H), 3.82 (s, 2H), 1.14(t, 7.1Hz, 3H)

Preparation Example 2: Preparation of 6-hydroxy-1-oxo-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

Step 1) Preparation of 2-(3-hydroxy-benzyl)-3-oxo-3-phenyl-propionic acid ethyl ester

Ethylbenzoyl acetate (27.6g, 161.28mmol), potassium carbonate (44.58g, 322.56mmol) and sodium iodide (29g, 193.53mmol) were dissolved in N,N-dimethyl formamide and the mixture was stirred for 1 hr at room temperature. 3-Chloromethylphenol (27.6g, 193.538mmol) was added thereto followed by stirring for 5hrs at room temperature. The resulting mixture was washed with saturated ammonium chloride and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 46.51mg of the titled compound (yield: 96%).

^{1}H-NMR (200MHz, $CDCl_3$) δ 7.99~7.94(m, 2H), 7.60~7.40(m, 3H) 7.23(m, 1H), 6.79~6.67(m, 3H), 4.65(m 1H), 4.20~4.05(m, 2H), 3.28(d, J=7.4Hz, 2H), 1.17~1.08(m, 3H)

Step 2) Preparation of 6-hydroxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

The compound (10g, 33.51mmol) obtained in Step 1 was mixed with poly phosphoric acid (100g), and stirred for 2hrs at room temperature. The resulting bright yellow solution was washed with water and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure to obtain a residue. Such a procedure was repeated seven times and residues obtained therefrom were combined and purified by flash chromatography to obtain 29.7g of the titled compound as a light yellow solid.

^{1}H-NMR (200MHz, $CDCl_3$) δ 7.45~7.39(m, 5H), 7.26(d, J=0.8Hz, 1H), 7.02(t, J=0.9Hz, 1H), 6.77(dd, J=8.2Hz, J=2.4Hz, 1H), 5.30(s, 1H), 4.13(q, J=7.2Hz, 2H), 3.81(s, 1H), 1.13(t, J=7.1Hz, 3H)

Step 3) Preparation of 6-hydroxy-1-oxo-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

The compound (16.00g, 57.07mmol) obtained in Step 2 was dissolved in 1,4-dioxane. Selenium dioxide (63.33g, 570.07mmol) was added thereto and refluxed for 10hrs, followed by cooling. The resulting mixture was washed with 1M sodium bicarbonate, and successively extracted with diethyl ether. The organic layer was separated, dried over anhydrous $MgSO_4$, and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 10.198g of the titled compound (yield: 61%) as a red solid.

^{1}H-NMR (200MHz, $CDCl_3$) δ 7.44~7.38 (m, 5H), 7.12 (d, J =8.4Hz, 1H), 7.02 (d, J =2.0Hz, 1H), 6.76 (dd, J =8.4, 2.0Hz, 1H), 4.12 (q, J =7.1Hz, 2H), 3.80 (s, 2H), 1.12 (t, J =7.1Hz, 3H)

Example 1) Preparation of 1-hydroxy-6-methoxy-1,3-diphenyl-1H-indene-2-carboxylic acid ethyl ester

Step 1) Preparation of 6-methoxy-1-oxo-3-phenyl-1H-indene-2-carboxylic acid

ethyl ester

6-Methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester (1g, 3.39 mmol) prepared in Preparation Example 1 was dissolved in 1,4-dioxane and selenium dioxide (5.65g, 50.96mmol) was added thereto. The mixture was refluxed for 24hrs, cooled, washed with 1M sodium bicarbonate, and extracted with diethyl ether. The organic layer was separated, dried over anhydrous $MgSO_4$, and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 756mg of the titled compound (yield: 72%) as a red solid.

^{1}H-NMR (200MHz, $CDCl_3$) δ 7.51(s, 5H), 7.19(d, J=2.4Hz, 1H), 7.08(d, J=8.2Hz, 1H), 6.83(dd, J=8.0Hz, J=2.2Hz, 1H), 4.18(q, J=7.1Hz, 2H), 3.86(s, 3H), 1.15(t, J=7.1Hz, 3H)

Step 2) Preparation of 1-hydroxy-6-methoxy-1,3-diphenyl-1H-indene-2-carboxylic acid ethyl ester

The compound (300mg, 0.97mmol) obtained in Step 1 was dissolved in THF and 1.5 equivalents of phenylmagnesium chloride were added thereto, followed by stirring for 1hr at 0°C. Then, the resulting mixture was washed with saturated saline, and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous $MgSO_4$, and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 285mg of the titled compound (yield: 76 %).

Example 2) Preparation of 1-hydroxy-6-methoxy-1-(3-methoxy-phenyl)-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

6-Methoxy-1-oxo-3-phenyl-1H-indene-2-carboxylic acid ethyl ester (100mg, 0.325mmol) obtained in Example 1 was dissolved in THF and 1.5 equivalents of 3-methoxyphenylmagnesium bromide were added thereto, followed

by stirring for 1hr at 0°C. Then, the reaction mixture was washed with saturated saline and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous $MgSO_4$, and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 122mg of the titled compound (yield: 90.4 %).

Example 3) Preparation of 1-hydroxy-isopropyl-6-methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

6-Methoxy-1-oxo-3-phenyl-1H-indene-2-carboxylic acid ethyl ester (300mg, 0.974mmol) obtained in Example 1 was dissolved in THF and 1.5 equivalents of isopropylmagnesium chloride were added thereto, followed by stirring for 1hr at 0°C. The resulting mixture was washed with saturated saline and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous $MgSO_4$, and concentrated under a reduced pressure. Then, the resulting residue was purified by flash chromatography to obtain 155mg of the titled compound (yield: 45.2 %).

Example 4) Preparation of 1-hydroxy-6-methoxy-1-methyl-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

6-Methoxy-1-oxo-3-phenyl-1H-indene-2-carboxylic acid ethyl ester (300mg, 0.974mmol) obtained in Example 1 was dissolved in THF and 1.2 equivalents of methylmagnesium chloride were added thereto, followed by stirring for 3hrs at 0°C. The resulting mixture was washed with saturated saline and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous $MgSO_4$, and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 126mg of the titled compound (yield: 38 %).

Example 5) Preparation of 1-benzyl-1-hydroxy-6-methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

6-Methoxy-1-oxo-3-phenyl-1H-indene-2-carboxylic acid ethyl ester (300mg, 0.974mmol) obtained in Example 1 was dissolved in THF and 1.2 equivalents of benzylmagnesium chloride were added thereto, followed by stirring for 3hrs at 0°C. The resulting mixture was washed with saturated saline and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous $MgSO_4$, and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 50mg of the titled compound (yield: 13 %).

Example 6) Preparation of 1-cyclohexyl-1-hydroxy-6-methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

6-Methoxy-1-oxo-3-phenyl-1H-indene-2-carboxylic acid ethyl ester (78mg, 0.253mmol) obtained in Example 1 was dissolved in THF, and 18%-cyclohexylmagnesium chloride (0.7mL, 0.506mmol) was added thereto, followed by stirring for 5hrs at 0°C. The resulting mixture was washed with saturated saline and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous $MgSO_4$, and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 30mg of the titled compound (yield: 30 %).

Example 7) Preparation of 1-hydroxy-1,3-diphenyl-6-(3-phenyl-propoxy)-1H-indene-2-carboxylic acid ethyl ester

Step 1) Preparation of 1-oxo-3-phenyl-6-(3-phenylpropoxy)-1H-indene-2-carboxylic acid ethyl ester

6-Hydroxy-1-oxo-3-phenyl-1H-indene-2-carboxylic acid ethyl ester (2g,

6.79mmol) prepared in Preparation Example 2, potassium carbonate (1.40g, 10.19mmol) and sodium iodide (0.2g, 1.39mmol) were dissolved in N,N-dimethyl formamide, and 1-bromo-3-phenyl propane (2.066ml, 13.592mmol) was added thereto, followed by stirring for 8hrs at room temperature. The resulting mixture was washed with saturated ammonium chloride and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous $MgSO_4$, and concentrated under a reduced pressure. Then, the resulting residue was purified by flash chromatography to obtain 2.37g of the titled compound (yield: 85 %) as a dark red solid.

^{1}H-NMR (200MHz, $CDCl_3$) δ 7.56(d, J=9Hz, 5H), 7.36~7.21(m, 6H), 7.09(d, J=8.2Hz, 1H), 6.83(dd, J=8.0Hz, J=2.4Hz, 1H), 4.26~4.16(m, 2H), 4.03(t, J=6.3Hz, 2H), 2.98~2.80(m, 2H), 2.22~2.07(m, 2H), 1.63~1.15(m, 3H)

Step 2) Preparation of 1-hydroxy-1,3-diphenyl-6-(3-phenyl-propoxy)-1H-indene-2-carboxylic acid ethyl ester

1-Oxo-3-phenyl-6-(3-phenyl-propoxy)-1H-indene-2-carboxylic acid ethyl ester (350mg, 0.85mmol) obtained in Step 1 was dissolved in THF, and phenylmagnesium chloride (0.064mL, 0.93mmol) was added thereto, followed by stirring for 1hr at 0°C. The resulting mixture was washed with saturated saline and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous $MgSO_4$, and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 475mg of the titled compound (yield: 100 %).

Example 8) Preparation of 1-hydroxy-6-(2-morpholine-4-yl-ethoxy)-1,3-diphenyl-1H-indene-2-carboxylic acid ethyl ester

Step 1) Preparation of 6-(2-morpholine-4-ylethoxy)-1-oxo-3-phenyl-1H-indene-2-

carboxylic acid ethyl ester

6-Hydroxy-1-oxo-3-phenyl-1H-indene-2-carboxylic acid ethyl ester (2g, 6.79mmol) prepared in Preparation Example 2 was dissolved in THF/benzene (270mL/90mL) solution, and 2-hydroxyethylmorpholine (5.83g, 44.45mmol) and triphenylphosphine (11.66g, 44.45mmol) were added thereto and kept at 0°C. Diisopropyl azodicarboxilate (8.99g, 44.45mmol) was added dropwise to the mixture, followed by stirring for 2hrs at room temperature. The resulting mixture was washed with saturated saline and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous $MgSO_4$, and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 14g of the titled compound (yield: 93 %) as a red solid.

^{1}H-NMR (200MHz, $CDCl_3$) δ 7.45(s, 5H), 7.18(d, J=2Hz, 1H), 7.07(d, J=7.8Hz, 1H), 6.84(m, 1H), 4.14～4.12(m, 4H), 2.80(t, J=5.6Hz, 2H), 2.78～2.57(m, 4H), 1.14(t, J=7.1Hz, 3H)

Step 2) Preparation of 1-hydroxy-6-(2-morpholine-4-yl-ethoxy)-1,3-diphenyl-1H-indene-2-carboxylic acid ethyl ester

6-(2-Morpholine-4-ylethoxy)-1-oxo-3-phenyl-1H-indene-2-carboxylic acid ethyl ester (1.5g, 3.68mmol) obtained in Step 1 was dissolved in THF, and phenylmagnesium chloride (3.865mL, 5.89mmol) was added thereto, followed by stirring for 2hrs at 0°C. The resulting mixture was washed with saturated saline and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous $MgSO_4$, and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 788mg of the titled compound (yield: 44 %).

Example 9) Preparation of 1-hydroxy-6-morpholine-4-ylmethyl-1,3-diphenyl-1H-indene-2-carboxylic acid ethyl ester

Step 1) Preparation of 3-oxo-3-m-tolylpropionic acid-ethyl ester

Sodium hydride (3.1g, 77.1mmol) and diethylcarbonate were added to 3-methyl acetophenone (4.5g, 33.54mmol). The reaction mixture was stirred for 2hrs with heating at 80°C. Once the reaction was completed, ice water and acetic acid were added thereto. The resulting mixture was washed with saturated saline and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 5.8g of the titled compound (yield: 84 %).

^{1}H-NMR (200MHz, $CDCl_3$) δ 7.83~7.63 (m, 2H) 7.42~7.28 (m, 2H) 4.27~4.18 (m, 2H) 3.97 (s, 2H) 2.40 (s, 3H) 1.36~1.23 (m, 3H)

Step 2) Preparation of 2-(3-methylbenzoyl)-3-phenyl acrylic acid ethyl ester

3-Oxo-3-m-tolylpropionic acid-ethyl ester (1g, 4.84mmol) obtained in Step 1 was dissolved in benzene, and benzaldehyde, acetic acid (0.15g, 2.49mmol) and piperidine (0.06g, 0.8mmol) were added thereto, followed by refluxing for 4hrs. Upon the completion of the reaction, the mixture was washed successively with saturated saline and saturated sodium bicarbonate, and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 1g of the titled compound (yield: 70 %).

^{1}H-NMR (200MHz, $CDCl_3$) δ 7.98 (s, 1H) 7.86~7.73 (m, 2H) 7.35~7.21 (m, 7H) 4.26~4.19 (m, 2H) 2.39 (s, 3H) 1.20~1.16 (m, 3H)

Step 3) Preparation of 5-methyl-3-oxo-1-phenylindene-2-carboxylic acid ethyl ester

2-(3-Methylbenzoyl)-3-phenyl acrylic acid ethyl ester (1g, 3.39mmol)

obtained in Step 2 was dissolved in dichloromethane, and methanesulfonic acid (5.22g, 54.35mmol) was added thereto, followed by stirring for 3hrs at RT. Once the reaction was completed, the mixture was cooled to 0°C, neutralized with sodium bicarbonate, and extracted with dichloromethane. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 273mg of the titled compound (yield: 27%).

^{1}H-NMR (200MHz, $CDCl_3$) δ 7.73~7.61 (m, 1H) 7.48~7.04 (m, 7H) 4.98~4.94 (m, 1H) 4.29~4.22 (m, 2H) 3.67~3.60 (m, 1H) 2.41 (s, 3H) 1.33~1.13 (m, 3H)

Step 4) Preparation of 6-methyl-1-oxo-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

Phenylselenyl chloride (72mg, 0.37mmol) was dissolved in dichloromethane and cooled to 0°C, and pyridine (32mg, 1.2mmol) was added thereto. The mixture was stirred for about 20 minutes. To the mixture, 5-methyl-3-oxo-1-phenylindene-2-carboxyl acid ethyl ester (100mg, 0.34mmol) obtained in Step 3 dissolved in methane was added, followed by stirring for 2hrs at RT. Once the reaction was completed, 10% hydrochloric acid (5mL) was added thereto and cooled to 0°C, and 30% peroxide (1mL) and water (5mL) were added thereto. The resulting mixture was extracted with dichloromethane. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 51mg of the titled compound (yield: 51%).

^{1}H-NMR (200MHz, $CDCl_3$) δ 7.51~7.04(m, 8H) 4.24~4.12(m, 2H) 2.39(s, 3H) 1.25~1.12(m, 3H)

Step 5) Preparation of 6-bromomethyl-1-oxo-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

6-Methyl-1-oxo-3-phenyl-1H-indene-2-carboxylic acid ethyl ester (3g, 10.3 mmol) obtained in Step 4 was dissolved in carbon tetrachloride, and N-bromosuccinimide (2g, 11.4mmol) and 2,2'-azobisisobutyronitrile (500mg, 3.09 mmol) were added thereto. The mixture was refluxed for 3hrs under the irradiation of a 375W tungsten lamp. Upon the completion of the reaction, the resulting mixture was washed with saturated saline and extracted with dichloromethane. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 1.4g of the titled compound (yield: 36.7%) in oil state.

^{1}H-NMR (200MHz, $CDCl_3$) δ 7.79~7.16 (m, 8H), 4.50 (s, 2H), 4.26 (q, J=7.1Hz, 2H), 1.16 (t, J=7.1Hz, 3H)

Step 6) Preparation of 6-morpholine-4-ylmethyl-1-oxo-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

6-Bromomethyl-1-oxo-3-phenyl-1H-indene-2-carboxylic acid ethyl ester (1.1g, 2.96mmol) obtained in Step 5 was dissolved in N,N-dimethyl formamide. Pyridine (264μl, 3.26mmol) and morpholine (284μl, 3.26mmol) were added thereto, followed by stirring for 2hrs. Upon the completion of the reaction, the resulting mixture was washed successively with saturated ammonium chloride and saline and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 180mg of the titled compound (yield: 16.1%) in red oil state.

^{1}H-NMR (200MHz, $CDCl_3$) δ 7.61~7.11 (m, 8H), 4.19 (q, J=7.1Hz, 2H), 3.70 (t, J=4.8Hz, 4H), 3.51 (s, 2H), 2.44 (t, J=4.8Hz, 4H), 1.15 (t, J=7.1Hz,

3H)

Step 7) Preparation of 1-hydroxy-6-morpholine-4-ylmethyl-1,3-diphenyl-1H-indene-2-carboxylic acid ethyl ester

6-Morpholine-4-yl-methyl-1-oxo-3-phenyl-1H-indene-2-carboxylic acid ethyl ester (30mg, 0.08mmol) obtained in Step 6 was dissolved in THF, and phenylmagnesium chloride (0.12mL, 0.24mmol) was added thereto, followed by stirring for 2hrs at 0°C. Upon the completion of the reaction, the mixture was washed with saturated saline and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 10mg of the titled compound (yield: 27%).

Example 10) Preparation of 1-hydroxy-1,3-diphenyl-6-(2-pyridine-2-yl-ethoxy)-1H-indene-2-carboxylic acid ethyl ester

6-Hydroxy-1-oxo-3-phenyl-1H-indene-2-carboxylic acid ethyl ester (300mg, 1.019mmol) obtained in Preparation Example 2 was dissolved in THF/benzene (30mL/10mL). 2-Pyridine ethanol (308mg, 2.039mmol) and triphenyl phosphine (534mg, 2.039mmol) were added thereto, and cooled to 0°C. Subsequently, diisopropyl azodicarboxilate (412mg, 2.039mmol) was slowly dropped thereto and stirred for 1hr at RT. The resulting mixture was washed with saturated saline and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 388g of 6-[2-(pyridine-2-yl)-ethoxy]-1-oxo-3-phenyl-1H-indene-2-carboxylic acid ethyl ester (yield: 89%) as a red solid.

Then, 1-oxo-3-phenyl-6-(2-pyridine-2-yl-ethoxy)-1H-indene-2-carboxylic acid ethyl ester (60mg, 0.15mmol) thus obtained was dissolved in THF and

phenylmagnesium chloride (0.15mL, 0.3mmol) was added thereto. The mixture was stirred for 5 minutes at RT, washed with sodium chloride solution and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 44mg of the titled compound (yield: 61%)

Example 11) Preparation of 1-hydroxy-1,3-diphenyl-6-(3-phenylpropoxy)-1H-indene-2-carboxylic acid ethyl ester

Step 1) Preparation of 3-phenyl-6-(3-phenyl-propoxy)-indene-1-one

3-Phenyl-1-[3-(3-phenyl-propoxy)-phenyl]-propenone (20g, 58.406mmol) and polyphosphoric acid (200g) were mixed and stirred for 6hrs at 45°C. The reaction mixture was washed with water and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography (ethyl acetate:hexane=1:5) to obtain 17.9g of the titled compound (yield: 81%) as a white solid.

^{1}H-NMR (200MHz, $CDCl_3$) δ 7.36~7.09 (m, 13H), 4.52 (dd, J =7.8, 3.6Hz, 1H), 4.01 (t, J =6.3Hz, 2H), 3.25 (dd, J =19.3, 7.7Hz, 1H), 2.81 (t, J =7.1Hz, 2H), 2.68 (dd, J =19.3, 3.6Hz, 1H), 2.14 (m, 2H)

Step 2) Preparation of 2-bromo-3-phenyl-6-(3-phenyl-propoxy)-indene-1-one

3-Phenyl-6-(3-phenyl-propoxy)-indene-1-one (200mg, 0.586mmol) obtained in Step 1 was dissolved in carbon tetrachloride, and N-bromosuccinimide (313mg, 1.75mmol) and 2,2'-azobisisobutyronitrile (9.7mg) were added thereto. The mixture was refluxed for 1hr under the irradiation of a 375W tungsten lamp. Upon the completion of the reaction, the mixture was washed with saturated saline

and extracted with dichloromethane. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography (ethyl acetate:hexane=1:5) to obtain 147mg of the titled compound (yield: 60%) as a red solid.

^{1}H-NMR (200MHz, $CDCl_3$) δ 7.69~7.16 (m, 11H), 7.02 (d, J =8.2Hz, 1H), 6.74 (dd, J =8.2, 2.3Hz, 1H), 3.97 (t, J =6.4Hz, 2H), 2.81 (t, J =6.3Hz, 2H), 2.11 (m, 2H)

Step 3) Preparation of 1-oxo-3-phenyl-6-(3-phenyl-propoxy)-1H-indene-2-carbonitrile

2-Bromo-3-phenyl-6-(3-phenyl-propoxy)-indene-1-one (1.0g, 2.3mmol) obtained in Step 2 was dissolved in N,N-dimethyl formamide (10mL), copper(I) cyanide (617mg, 6.9mmol) was added thereto, and the mixture was stirred for 3hrs at 150°C, followed by cooling. The resulting mixture was washed with saturated ammonium chloride and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography (ethyl acetate:hexane=1:3) to obtain 700mg of the titled compound (yield: 80%) as a red solid.

^{1}H-NMR (200MHz, $CDCl_3$) δ 7.83~7.18 (m, 12H), 6.89(dd, J =8.2, J =2.3Hz, 1H), 4.02(t, J =6.5Hz, 2H), 2.81(t, J =6.3Hz, 2H), 2.13(m, 2H)

Step 4) Preparation of 1-hydroxy-1,3-diphenyl-6-(3-phenylpropoxy)-1H-indene-2-carboxylic acid ethyl ester

1-Oxo-3-phenyl-6-(3-phenyl-propoxy)-1H-indene-2-carbonitrile (100mg, 0.274mmol) obtained in Step 3 was dissolved in THF under a N_2 gas atmosphere, and phenylmagnesium chloride (2M sol, 0.131μL) was added thereto, followed by stirring for 2hrs at 0°C. The resulting mixture was washed with saturated

ammonium chloride and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure. Then, the resulting residue was purified by flash chromatography to obtain 80.7mg of the titled compound (yield: 66%) as a pink solid.

^{1}H -MR (200MHz, $CDCl_3$) δ 7.70～6.90 (m, 18H), 3.95 (t, J=6.2Hz, 2H), 2.77 (t, J=7.4Hz, 2H), 2.10～2.04 (m, 2H)

Example 12) Preparation of 1-hydroxy-1,3-diphenyl-6-(3-phenyl-propoxy)-1H-indene-2-carboxylic acid methyl ester

Step 1) Preparation of 1-oxo-3-phenyl-6-(3-phenyl-propoxy)-1H-indene-2-carboxylic acid methyl ester

1-Oxo-3-phenyl-6-(3-phenylpropoxy)-1H-indene-2-carboxylic acid ethyl ester (2g, 4.85mmol) obtained in Example 7 was dissolved in methanol, p-toluenesulfonic acid (92mg, 0.49mmol) was added thereto, and refluxed for 24hrs. The resulting mixture was washed with sodium bicarbonate and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure. Then, the resulting residue was purified by flash chromatography to obtain 1.2g of the titled compound (yield: 62%).

^{1}H-NMR (200MHz, $CDCl_3$) δ 7.51～6.78 (m, 13H), 4.01 (t, J=6.0 Hz, 2H), 3.72 (s, 3H), 2.81 (t, J=7.2, 2H), 2.11 (m, 2H)

Step 2) Preparation of 1-hydroxy-1,3-diphenyl-6-(3-phenyl-propoxy)-1H-indene-2-carboxylic acid methyl ester

1-Oxo-3-phenyl-6-(3-phenylpropoxy)-1H-indene-2-carbonitrile (350mg, 0.878mmol) obtained in Step 1 was dissolved in THF, and phenylmagnesium chloride (0.483mL, 0.966mmol) was added thereto, followed by stirring for 3hrs at 0°C. Upon the completion of the reaction, the mixture was washed with

saturated saline and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 378mg of the titled compound (yield: 90%).

Example 13) Preparation of 1-hydroxy-6-methoxy-1,3-diphenyl-1H-indene-2-carboxylic acid

1-Hydroxy-6-methoxy-1,3-diphenyl-1H-indene-2-carboxylic acid ethyl ester (110mg, 0.285mmol) prepared in Example 1 was dissolved in THF, and an excess amount of sodium hydroxide dissolved in aqueous ethanol was added thereto in such a way not to cause layer separation. The mixture was stirred for 24hrs at RT, and the pH was adjusted to 3~4 using 2N hydrochloric acid. The resulting mixture was extracted with ethyl acetate. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure, to obtain 99mg of the titled compound (yield: 97%).

Example 14) Preparation of 1-hydroxy-6-methoxy-1-methyl-3-phenyl-1H-indene-2-carboxylic acid

1-Hydroxy-6-methoxy-1-methyl-3-phenyl-1H-indene-2-carboxylic acid ethyl ester (100mg, 0.309mmol) prepared in Example 4 was dissolved in THF, and an excess amount of sodium hydroxide dissolved in aqueous ethanol was added thereto in such a way not to cause layer separation. The mixture was stirred for 24hrs at RT, and the pH was adjusted to 3~4 using 2N hydrochloric acid. The resulting mixture was extracted with ethyl acetate. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure, to obtain 63mg of the titled compound (yield: 69%).

Example 15) Preparation of 1-benzyl-1-hydroxy-6-methoxy-3-phenyl-1H-indene-

2-carboxylic acid

1-Benzyl-1-hydroxy-6-methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester (35mg, 0.087mmol) prepared in Example 5 was dissolved in THF, and an excess amount of sodium hydroxide dissolved in aqueous ethanol was added thereto in such a way not to cause layer separation. The mixture was stirred for 24hrs at RT, and the pH was adjusted to 3~4 using 2N hydrochloric acid. The resulting mixture was extracted with ethyl acetate. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure, to obtain 35mg of the titled compound (yield: 100%).

Example 16) Preparation of 1-hydroxy-1,3-diphenyl-6-(3-phenyl-propoxy)-1H-indene-2-carboxylic acid

1-Hydroxy-1,3-diphenyl-6-(3-phenyl-propoxy)-1H-indene-2-carboxylic acid ethyl ester (200mg, 0.408mmol) prepared in Example 7 was dissolved in THF, and an excess amount of sodium hydroxide dissolved in aqueous ethanol was added thereto in such a way not to cause layer separation. The mixture was stirred for 5hrs at RT, and the pH was adjusted to 3~4 using 2N hydrochloric acid. The resulting mixture was extracted with ethyl acetate. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure, to obtain 85mg of the titled compound (yield: 45%).

Example 17) Preparation of 1-cyclohexyl-1-hydroxy-6-methoxy-3-phenyl-1H-indene-2-carboxylic acid

1-Cyclohexyl-1-hydroxy-6-methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester (20mg, 0.051mmol) prepared in Example 6 was dissolved in THF, and an excess amount of sodium hydroxide dissolved in aqueous ethanol was added thereto in such a way not to cause layer separation. The mixture was stirred for 24hrs at RT, and the pH was adjusted to 3~4 using 2N hydrochloric acid. The

resulting mixture was extracted with ethyl acetate. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure, to obtain 15mg of the titled compound (yield: 80%).

Example 18) Preparation of 1,6-dimethoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

Step 1) Preparation of 1-bromo-6-methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

6-Methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester (1.5g, 5.10mmol) prepared in Preparation Example 1 was dissolved in dichloromethane (80mL), and N-bromosuccinimide (1.09g, 6.12mmol) and 2,2'-azobisisobutyronitrile (0.08mg, 0.51mmol) were added thereto. The mixture was stirred for 2 hrs at RT under the irradiation of a 375W tungsten lamp. Upon the completion of the reaction, the mixture was washed with saturated saline and extracted with dichloromethane. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography (ethyl acetate/n-hexane=1/20 → 1/9) to obtain 1.4g of the titled compound (yield: 74%) as a yellow solid.

^{1}H-NMR (300MHz, $CDCl_3$) δ 7.46-7.42 (m, 5H) 7.21 (d, J = 2.4 Hz, 1H) 7.13 (d, J = 8.4 Hz, 1H) 6.86 (dd, J = 8.4, 2.4 Hz, 1H) 5.85 (s, 1H) 4.25-4.10 (m, 2H) 3.88 (s, 3H) 1.15 (t, J = 7.2 Hz, 3H)

Step 2) Preparation of 1,6-dimethoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

1-Bromo-6-methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester (60mg, 0.18mmol) obtained in Step 1 was dissolved in methanol (10mL), silver nitrate (37.20mg, 0.22mmol) was added thereto, stirred for 3hrs at RT, and filtered.

The organic layer was separated, and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 14mg of the titled compound (yield: 24%).

Example 19) Preparation of 1-ethoxy-6-methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

1-Bromo-6-methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester (30mg, 0.09mmol) obtained in Example 18 was dissolved in ethanol (3mL), silver nitrate (15.50mg, 0.09mmol) was added thereto, stirred for 3.5hrs at RT, and filtered. The organic layer was separated, and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 16mg of the titled compound (yield: 52%).

Example 20) Preparation of 1-amino-6-methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

Step 1) Preparation of 1-hydroxyimino-6-methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

6-Methoxy-1-oxo-3-phenyl-1H-indene-2-carboxylic acid ethyl ester (1.6g, 5.19mmol) obtained in Example 1 was dissolved in ethanol (100mL), hydroxylamine hydrochloride (1.08g, 15.57mmol) and pyridine (1.64g, 1.68mL, 20.76mmol) were added thereto, refluxed for 1hr, and cooled to RT. The resulting mixture was washed with saturated sodium bicarbonate and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 1.34g of the titled compound (yield: 80%).

^{1}H-NMR (300MHz, $CDCl_3$) δ 11.41 (brs, 1H) 8.10 (d, J = 2.4 Hz, 1H) 7.47-

7.42 (m, 5H) 7.12 (d, J = 8.4 Hz, 1H) 6.88 (dd, J = 8.4, 2.4 Hz, 1H) 4.17 (q, J = 14.4, 7.2 Hz, 2H) 3.89 (s, 3H) 1.06 (t, J = 7.2 Hz, 3H)

Step 2) Preparation of 1-amino-6-methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

1-Hydroxyimino-6-methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester (1.00g, 3.09mmol) obtained in Step 1 was dissolved in methanol (100mL), and 10%-palladium (583mg) was added thereto. The mixture was stirred for 15hrs at RT while providing H_2 gas thereto using a balloon, filtered through celite, and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 786mg of the titled compound (yield: 82%).

Example 21) Preparation of 1-amino-3-phenyl-6-(3-phenyl-propoxy)-1H-indene-2-carboxylic acid ethyl ester

Step 1) Preparation of 1-hydroxyimino-3-phenyl-6-(3-phenylpropoxy)-1H-indene-2-carboxylic acid ethyl ester

1-Oxo-3-phenyl-6-(3-phenyl-propoxy)-1H-indene-2-carboxylic acid ethyl ester (1.5g, 3.64mmol) obtained in Example 7 was dissolved in ethanol (100mL), hydroxylamine hydrochloride (759mg, 10.92mmol) and pyridine (1.15g, 15.56 mmol) were added thereto, refluxed for 1hr, and cooled to RT. The resulting mixture was washed with saturated sodium bicarbonate and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 0.91g of the titled compound (yield: 58%).

^{1}H-NMR (300MHz, $CDCl_3$) δ 11.3 (brs, 1H) 8.10 (d, J = 2.4 Hz, 1H) 7.47-7.42 (m, 10H) 7.12 (d, J = 8.4 Hz, 1H) 6.88 (dd, J = 8.4, 2.4 Hz, 1H) 4.17 (q, J = 7.2 Hz, 2H) 4.04 (t, J = 6.8 Hz, 2H) 2.83 (t, J = 6.8 Hz, 2H) 2.11 (quint, J = 6.8 Hz,

2H) 1.06 (t, J = 7.2 Hz, 3H)

Step 2) Preparation of 1-amino-3-phenyl-6-(3-phenyl-propoxy)-1H-indene-2-carboxylic acid ethyl ester

1-Hydroxyimino-3-phenyl-6-(3-phenylpropoxy)-1H-indene-2-carboxylic acid ethyl ester (0.5g, 1.17mmol) obtained in Step 1 was dissolved in methanol (30mL) and 10%-palladium (400mg) was added thereto. The mixture was stirred for 15hrs at RT while providing H_2 gas thereto using a balloon, filtered through celite, and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 377mg of the titled compound (yield: 78%).

Example 22) Preparation of 1-amino-6-(2-morpholine-4-yl-ethoxy)-3-phenyl-1H-indene-2-carboxylic acid cyclohexylamide

Step 1) Preparation of 6-hydroxy-1-oxo-3-phenyl-1H-indene-2-carboxylic acid methyl ester

6-Hydroxy-1-oxo-3-phenyl-1H-indene-2-carboxylic acid ethyl ester (500mg, 1.70 mmol) prepared in Preparation Example 2 was dissolved in methanol (30mL), p-toluenesulfonic acid (65mg, 0.34mmol) was added thereto, refluxed for 24hrs, and the solvent was removed therefrom by evaporation. The resulting residue was purified by flash chromatography to obtain 470mg of the titled compound (yield: 98.6%) as a red solid.

^{1}H-NMR (300MHz, $CDCl_3$) δ 7.75 ~ 6.81(m, 8H), 3.73(s, 3H)

Step 2) Preparation of 6-hydroxy-1-oxo-3-phenyl-1H-indene-2-carboxylic acid

6-Hydroxy-1-oxo-3-phenyl-1H-indene-2-carboxylic acid methyl ester (2.6g, 9.28mmol) obtained in Step 1 was dissolved in dichloroethane, and boron

tribromide methyl sulfide (6.0mL, 27.84mmol) was added thereto. The mixture was refluxed for 2hrs at 90°C, cooled in an ice bath, neutralized using sodium bicarbonate, and adjusted to pH 2 using 6N hydrochloric acid. The resulting mixture was washed successively with dichloromethane and water. The organic layer was separated, dried over anhydrous $MgSO_4$, concentrated under a reduced pressure and recrystallized to obtain 1.2g of the titled compound (yield: 48.6%).

^{1}H-NMR (300MHz, $CDCl_3$) δ 7.79～6.84(m, 8H)

Step 3) Preparation of 6-hydroxy-1-oxo-3-phenyl-1H-indene-2-carboxylic acid cyclohexylamide

6-Hydroxy-1-oxo-3-phenyl-1H-indene-2-carboxylic acid (100mg, 0.38mmol) obtained in Step 2 was dissolved in dichloromethane, and triethylamine (175μl, 1.25mmol) and cyclohexylamine (43μl, 0.38mmol) were added thereto at 10°C. Then, bis(2-oxo-3-oxazoline)phosphoryl chloride (100mg, 0.38mmol) was further added thereto, stirred for 10~20 minutes at RT, and then stirred for additional 1hr in a water bath. After water was added to complete the reaction, the mixture was washed with sodium bicarbonate and extracted with dichloromethane. The organic layer was separated, dried over anhydrous $MgSO_4$, concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 26mg of the titled compound (yield: 20.0%) as a red solid.

^{1}H-NMR (300MHz, $CDCl_3$) δ 7.68～6.80 (m, 8H), 3.87 (m, 1H), 1.80～1.34 (m, 10H)

Step 4) Preparation of 6-(2-morpholine-4-ylethoxy)-1-oxo-3-pheny-1H-indene-2-carboxylic acid cyclohexylamide

6-Hydroxy-1-oxo-3-phenyl-1H-indene-2-carboxylic acid cyclohexylamide (141mg, 0.41mmol) obtained in Step 3 was dissolved in

tetrahydropuran/benzene (3mL/2mL), and 4-(2-hydroxyethyl)morpholine (99μl, 0.82mmol) and triphenylphosphine (215mg, 0.82mmol) were added thereto. Then, diisopropyl azodicarboxilate (149μl, 0.82mmol) was added slowly thereto at 0°C, and stirred for 2hrs at RT. The resulting mixture was washed with saturated saline and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 165mg of the titled compound (yield: 88.3%).

^{1}H-NMR (200MHz, $CDCl_3$) δ 7.92~6.85 (m, 8H), 4.16 (t, J=5.4Hz, 2H), 3.86(m, 1H), 3.73 (t, J=4.8Hz, 4H), 2.82 (t, J=5.4Hz, 2H) 2.57 (t, J=4.8Hz, 4H), 1.81~1.34 (m, 10H)

Step 5) Preparation of 1-amino-6-(2-morpholine-4-yl-ethoxy)-3-phenyl-1H-indene-2-carboxylic acid cyclohexylamide

6-(2-Morpholine-4-ylethoxy)-1-oxo-3-pheny-1H-indene-2-carboxylic acid cyclohexylamide (130mg, 0.28%) obtained in Step 4 was dissolved in ethanol (20 mL), and hydroxylamine hydrochloride (60mg, 0.85mmol) and pyridine (892mg, 1.13mmol) were added thereto. The mixture was refluxed for 1hr, and cooled to RT, and extracted with dichloromethane. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 86mg of 1-hydroxyimino-6-(2-morpholine-4-yl-ethoxy)-3-pheny-1H-indene-2-carboxylic acid cyclohexylamide (yield: 64%). Subsequently, 1-hydroxyimino-6-(2-morpholine-4-yl-ethoxy)-3-pheny-1H-indene-2-carboxylic acid cyclohexylamide (80mg, 0.17mmol) thus obtained was dissolved in methanol (20mL) and 10%-palladium (100mg) was added thereto. The mixture was stirred for 15hrs at RT while providing H_2 gas thereto using a balloon, filtered through celite, and concentrated under a reduced pressure. Then, the resulting residue was purified

by flash chromatography to obtain 14mg of the titled compound (yield: 18%).

Example 23) Preparation of 1-amino-3-phenyl-6-(3-phenyl-propoxy)-1H-indene-2-carbonitrile

1-Oxo-3-phenyl-6-(3-phenyl-propoxy)-1H-indene-2-carbonitrile (293mg, 0.80mmol) obtained in Example 11 was dissolved in ethanol (20mL), and hydroxylamine hydrochloride (167mg, 2.41mmol) and pyridine (254mg, 3.21 mmol) were added thereto, refluxed for 3hrs, and cooled to RT. The resulting mixture was washed with saturated sodium bicarbonate, extracted with ethyl acetate. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 230mg of 1-hydroxyimino-3-phenyl-6-(3-phenyl-propoxy)-1H-indene-2-carbonitrile (yield: 75%). Subsequently, 1-hydroxyimino-3-phenyl-6-(3-phenyl-propoxy)-1H-indene-2-carbonitrile (230mg, 0.60mmol) thus obtained was dissolved in methanol (20mL), and 10%-palladium (230mg) was added thereto. The mixture was stirred for 15hrs at RT while providing H_2 gas thereto using a balloon, filtered through celite, and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 90mg of the titled compound (yield: 41%).

Example 24) Preparation of 1-acetylamino-6-methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

1-Amino-6-methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester (60mg, 0.19mmol) prepared in Example 20 was dissolved in dichloromethane (10 mL), and acetyl chloride (76.15mg, 70.0 μl, 0.97mmol) and triethylamine (130.00mg, 0.18mL, 128mmol) were added thereto in order at 0°C. The mixture was stirred for 1hr at RT, washed with saturated saline and extracted with dichloromethane. The organic layer was separated, dried over anhydrous $MgSO_4$

and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 48mg of the titled compound (yield: 71%).

Example 25) Preparation of 6-methoxy-3-phenyl-1-propionylamino-1H-indene-2-carboxylic acid ethyl ester

1-Amino-6-methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester (50mg, 0.16mmol) prepared in Example 20 was dissolved in dichloromethane (10 mL), and propionyl chloride (150.38mg, 0.14mL, 1.62mmol) and triethylamine (180.12mg, 0.25mL, 1.78mmol) were added thereto in order at 0°C. The mixture was stirred for 24hrs at RT, and an excess amount of propionyl chloride (2mL) was further added thereto to be stirred for 15hrs. The resulting mixture was washed with saturated saline and extracted with dichloromethane. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 29mg of the titled compound (yield: 50%).

Example 26) Preparation of 1-acetylamino-3-phenyl-6-(3-phenyl-propoxy)-1H-indene-2-carboxylic acid ethyl ester

1-Amino-3-phenyl-6-(3-phenyl-propoxy)-1H-indene-2-carboxylic acid ethyl ester (30mg, 0.07mmol) prepared in Example 21 was dissolved in dichloromethane (10mL), and acetyl chloride (30.15mg, 0.37mmol) and triethylamine (40mg, 0.37mmol) were added thereto in order at 0°C. The mixture was stirred for 24hrs at RT, washed with saturated saline and extracted with dichloromethane. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 15mg of the titled compound (yield: 45%).

Example 27) Preparation of 1-acetylamino-6-(2-morpholine-4-yl-ethoxy)-3-phenyl-1H-indene-2-carboxylic acid cyclohexylamide

1-Amino-6-(2-morpholine-4-yl-ethoxy)-3-phenyl-1H-indene-2-carboxylic acid cyclohexylamide (14mg, 0.03mmol) prepared in Example 22 was dissolved in dichloromethane (10mL), acetyl chloride (24mg, 0.3mmol) and triethylamine (30mg, 0.3mmol) were added thereto in order at 0°C, and stirred for 24hrs at RT. The resulting mixture was washed with saturated saline and extracted with dichloromethane. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 3mg of the titled compound (yield: 20%).

Example 28) Preparation of 1-diethylamine-6-methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

1-Bromo-6-methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester (100mg, 0.27mmol) obtained in Example 18 was dissolved in THF (10mL), and diethylamine (98.74mg, 0.14mL, 1.35mmol) was added dropwise thereto. The mixture was stirred for 12hrs at RT, and the solvent was removed under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 65mg of the titled compound (yield: 66.3%).

Example 29) Preparation of 1-ethylamino-6-methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

1-Bromo-6-methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester (100mg, 0.27mmol) obtained in Example 18 was dissolved in THF (10mL), and 2.0 M ethylamine (0.68mL, 1.35mmol) in THF was added dropwise thereto. The mixture was stirred for 12hrs at RT, and the solvent was removed under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 68mg of the titled compound (yield: 75.6%).

Example 30) Preparation of 6-methoxy-1-morpholine-4-yl-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

1-Bromo-6-methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester (150mg, 0.40mmol) obtained in Example 18 was dissolved in THF (15mL), and morpholine (175.01mg, 0.18mL, 2.01mmol) was added dropwise thereto. The mixture was stirred for 12hrs at RT, and the solvent was removed under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 126mg of the titled compound (yield: 83%).

Example 31) Preparation of 1-benzylamino-6-methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

1-Bromo-6-methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester (120mg, 0.32mmol) obtained in Example 18 was dissolved in THF (10mL), and benzylamine (102.87mg, 0.11mL, 0.93mmol) and sodium iodide (9.60 mg, 0.06 mmol) were added thereto, followed by refluxing for 6hrs. The resulting mixture was washed with saturated saline and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure. The resulting residue was purified by flash chromatography to obtain 56mg of the titled compound (yield: 44%).

Example 32) Preparation of 1-cyclohexylamino-6-methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester

1-Bromo-6-methoxy-3-phenyl-1H-indene-2-carboxylic acid ethyl ester (100mg, 0.27mmol) obtained in Example 18 was dissolved in THF (10mL), and cyclohexylamine (132.86mg, 0.15mL, 1.34mmol) was added dropwise thereto. The mixture was stirred for 12hrs at RT, and the solvent was removed under a reduced pressure. The resulting residue was purified by flash chromatography to

obtain 25mg of the titled compound (yield: 24%).

Formulation Example 1: Preparation of syrup

A syrup containing hydrochloric acid salt of the compound of Example 8, 1-hydroxy-6-(2-morpholine-4-yl-ethoxy)-1,3-diphenyl-1H-indene-2-carboxylic acid ethyl ester, was prepared using the ingredients shown in Table 2 by dissolving 1-hydroxy-6-(2-morpholine-4-yl-ethoxy)-1,3-diphenyl-1H-indene-2-carboxylic acid ethyl ester hydrochloride, saccharine, and sugar in warm water, cooling, and adding other ingredients thereto to a volume of 100mL.

Table 2

Ingredients	Quantity
1-Hydroxy-6-(2-morpholine-4-yl-ethoxy)-1,3-diphenyl-1H-indene-2-carboxylic acid ethyl ester hydrochloride	2g
Saccharine	0.8g
Sugar	25.4g
Glycerine	8.0g
Flavoring	0.04g
Ethanol	4.0g
Sorbic Acid	0.4g
Distilled Water	q.s.

Formulation Example 2: Preparation of tablet

A tablet containing hydrochloric acid salt of the compound of Example 8 was prepared with the ingredients shown in Table 3 by mixing 1-hydroxy-6-(2-morpholine-4-yl-ethoxy)-1,3-diphenyl-1H-indene-2-carboxylic acid ethyl ester hydrochloride with lactose, potato starch and colloidal silica and adding a 10% gelatin solution thereto. Then the mixture was crushed, sieved through a 14

mesh and dried. Finally the remaining ingredients were added thereto and tableting was performed.

Table 3

Ingredients	Quantity
1-Hydroxy-6-(2-morpholine-4-yl-ethoxy)-1,3-diphenyl-1H-indene-2-carboxylic acid ethyl ester hydrochloride	250g
Lactose	175.9g
Potato Starch	180g
Colloidal Silica	32g
10% gelatin solution	25g
Potato Starch	160g
Talc	50g
Magnesium Stearate	5g.

Formulation Example 3: Preparation of an injectable solution

1-Hydroxy-6-(2-morpholine-4-yl-ethoxy)-1,3-diphenyl-1H-indene-2-carboxylic acid ethyl ester hydrochloride, sodium chloride and ascorbic acid were dissolved in distilled water in amounts as shown in Table 4 and sterilized.

Table 4

Ingredients	Quantity
1-Hydroxy-6-(2-morpholine-4-yl-ethoxy)-1,3-diphenyl-1H-indene-2-carboxylic acid ethyl ester hydrochloride	1g
Sodium chloride	0.6g
Ascorbic acid	0.1g
Distilled water	q.s.

Test Example 1: PPARγ activation test

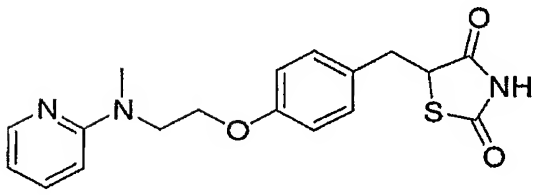
The activity for PPARγ activation was examined as follows.

The vector fused with ligand binding domain of a human PPARγ gene and DNA binding site of a yeast GAL-4 gene, and luciferase reporter vector were simultaneously transfected in NIH/3T3 cell. The cells were cultured for 24hrs. The solution containing the cells at a concentration of 2×10^4 cells/well was placed on a 96-well plate. Then, each of the test compounds of the present invention and the control group without test compounds was added thereto. After incubating for 24hrs, the cells were subjected to lysis. The luciferase activity of the resultant was then measured, and the activation activity of the test compound was expressed as EC_{50} (the concentration at which 50% of the maximum activation was observed) to compute the activation intensities of the test compounds and the comparative compound, rosiglitazone, relative to PPARγ. The results are shown in Table 5.

Rosiglitazone having the formula (XVI) was prepared according to the method described in *J. Med. Chem.* **1994**, 37, 3997.

Table 5

Compound	EC_{50} (nM)
3	250
4	230
5	95
6	50
7	25
8	75
10	150
11	100
15	230
18	45
19	20
24	50
25	12
26	40
32	250
Rosiglitazone	300



(XVI)

As shown in Table 5, the inventive compounds exhibited superior PPARγ activities over the comparative compound, rosiglitazone.

Test Example 2: Effectiveness in lowering blood glucose level

The effectiveness in lowering blood glucose level of the inventive compound was examined using ob/ob mice (male, 8-9 week old), a type 2 diabetes model animals which expresses signs of hyperglycemia and hyperinsulinemia, bred in house facilities of Korea Research Institute of Chemical Technology.

The hydrochloric acid salt of 1-hydroxy-6-(2-morpholine-4-yl-ethoxy)-1,3-diphenyl-1H-indene-2-carbo-xylic acid ethyl ester prepared in Example 8 was suspended in saline/0.2% Tween® 80. The resulting solution was intraperitoneally administered to the mice at a dose of 50 mg/kg, once a day for 5 days, or orally administered to the mice, at a dose of 100 mg/kg, twice a day for 14 days. Days 1, 3 and 5 were selected for intraperitoneal administration, and days 5, 10 and 14, for oral administration, to collect blood samples for measuring the blood glucose levels. The extent of inhibition of the inventive compound relative to the control (saline-0.2% Tween 80 in the absence of the compound) is shown in Table 6. Upon the completion of the oral administration for 14 days, the mice were fasted for 16hrs to perform OGTT(Oral Glucose Tolerance Test) to determine the changes in insulin sensitivity induced by the oral administration. After administrating glucose to the mice at a dose of 2g/kg orally, blood samples were collected at 0, 15, 30 60 and 120 minutes to measure blood glucose levels. The change in the total amount of blood glucose was computed over the 120 minute period to assess the extent of enhancing glucose clearance rates by the compound treatment. The results are shown in Table 6, as % inhibition of total amount of blood glucose by the compound treatment relative to the untreated group.

Table 6

Classification	Extent of Inhibition (%)
Intraperitoneal Administration (50mg/kg/day)	32.0
Oral Administration (100mg/kg/day)	23.7
Oral Glucose Tolerance Test (Blood Glucose)	10.2

Moreover, C57/BL6J mice (male, 4 week old) which received high fat diet (60% fat) for 10-11 weeks and showed hyperglycemia and insulin resistance were chosen to carry out similar experiments (oral administration for 14 days but once a day) as described above. The extents of suppression of blood glucose and insulin levels were measured as mentioned above. The results are shown in Table 7. To check possible adverse side effects caused by the administration of the compound, the weight, heart weight and liver weight of each mouse were measured. GPT and GOT values were also calculated by employing a kit available in the market. The results are listed in Table 8.

Table 7

Classification	Inhibition Ratio (%)
Blood glucose level	30.0
Blood Insulin level	44.6
Oral Glucose Tolerance Test	23.8(Glucose)/56.2(Insulin)

Table 8

	Weight (g)	Heart Weight (g)	Liver Weight (g)	GPT / GOT (karmen)
Standard (high-fat diet)	40 ± 2.0	0.133 ±0.012	1.42 ± 0.11	52 ± 10 / 48 ±11
The Inventive Compound	37 ± 2.0	0.117 ±0.012	1.22 ± 0.10	47 ± 6.5 /35±6.2
Rosiglitazone	40 ± 1.6	0.133 ±0.004	1.35 ± 0.14	79 ± 8.3/40 ±7.1

As shown in Tables 6, 7, and 8, the inventive compound has an excellent effect in lowering both blood glucose and insulin levels, when it is administered by either orally or intraperitoneally with no side effects such as weight gain, hepatotoxicity or cardiotoxicity.

While the invention has been described with respect to the above specific embodiments, it should be recognized that various modifications and changes may be made to the invention by those skilled in the art which also fall within the scope of the invention as defined by the appended claims.